Original Research Article

The lipid profile of Human Immunodeficiency Virus-infected patients receiving antiretroviral therapy at Mpilo Central Hospital Opportunistic Infections Clinic

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ABSTRACT

Aims:

Long term use of antiretroviral therapy subpopulation living with human immunodeficiency virus is associated with disturbances in blood lipids profiles which are not routinely monitored. More data on such disturbances are needed to persuade the country program to institute routine monitoring. This study sought to determine the prevalence and timing of dyslipidaemia in HIV/AIDS naïve people on ART at in Zimbabwe.

Place and Duration of Study: The study was conducted at Mpilo Central Hospital Opportunistic Infections Clinic in Bulawayo, Zimbabwe over a period of three months.

Methods

A cross-sectional study was conducted in HIV-infected persons receiving highly active anti-retroviral treatment at Mpilo Central Hospital Opportunistic Infections Clinic. Lipid assays were determined by Elisa methods. Viral loads and CD4 were measured using the COBAS® TaqMan® and BD FACSCount™ Flow Cytometer, respectively.

Results

A total of 149 consenting participants were enrolled and most (63.2%) were females. The median age of the respondents was 43 years and their median CD4 count was 436 cells/µl after a median duration on ART of 36 months. Viral load was <40 in the majority (68.6%) of the participants. More females (63.1%) were on HAART and were aged >35 (60.4%) years. NNRTI (90.6%) were the more commonly prescribed HAART. The prevalence of dyslipidaemia was 70.2%. Hypercholesterolaemia was observed in 72 (48.3%) patients with 26 being male and 46 being female. High levels of LDL-cholesterol (LDL-c ≥ 3.0 mmol/L) were found in 115 patients with 74 of them being female. Hypertriacylglycerolaemia (TAG ≥ 2.0 mmol/L) was present in 8 cases. The proportion of patients with a low HDL-cholesterol (HDL-c < 1.0 mmol/L) was 15.3% while those with a ratio of TC/HDL-c ≥ 4.1 were 87.5%.

Conclusion

The study demonstrated a high prevalence of dyslipidaemia in HIV-patients receiving HAART. There is a need for the country HIV program to institute laboratory monitoring of blood lipids in patients over one year on HAART.

Key words: Dyslipidaemia, High active antiretroviral therapy, Human immunodeficiency virus/ Acquired immunodeficiency syndrome, Hypercholesterolaemia, Hypertriacylglycerolaemia,

INTRODUCTION

Serum lipid profiles have a multifactorial etiology that is determined by a large number of environmental and genetic factors. Genetic and dietary factors influence serum cholesterol concentration, but detailed mechanisms of their interactions are not well known. An increase in dietary cholesterol intake raises serum cholesterol concentrations in some but not all subjects.

Human immunodeficiency virus (HIV) infected patients tend to develop dyslipidemia even before commencement of treatment [1, 2]. Serum tests reveals highly atherogenic lipid profiles with increased levels of total cholesterol, low-density lipoprotein cholesterol (LDL-

C), and triacylglycerols (TG) and decreased levels of high-density lipoprotein cholesterol (HDL-C) compared to HIV-negative individuals [1, 3-5]. The pathogenesis of dyslipidemia in HIV-1 infection is complex and involves factors related to the virus, the host, and to the antiretroviral therapy (ART) [6]. Researchers have shown the association of HIV infection and ART with accelerated atherosclerosis and an increased number of cases of myocardial infarction [7]. HAART consists of a combination of drugs that inhibit different stages of viral replication, and it is divided mechanistically into six classes [7] based on whether it targets the viral lifecycle or viral enzymes: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitor (enfuvirtide or T-20), entry inhibitor chemokine receptor 5 (CCR5) antagonist maraviroc, and HIV-1 integrase strand transfer inhibitor [8, 9].

The introduction of HAART has resulted in an significant increase in life expectancy of HIV infected individuals [10]**.** Incidences of deaths due to non-HIV-related deaths in this sub-population remained high owing to side effects of the drugs which also results in development of dyslipidemia [11, 12]. HAART are used to suppresses HIV infection causing immune system recovery which may be accompanied by increases in lipid profiles as the HIV-positive individual return to wellness [13, 14]**.** Studies have shown association of PI's use with hypertriacylglycerolaemia and hypercholesterolemia with ritonavir having been shown to increase TAG's and LDC-C after 2 weeks in healthy volunteers [15, 16]. There is a nuclear transcription factor that is responsible for the regulation of expression of many lipid metabolic genes which is called sterol response element binding protein (SREBP). This tends to accumulate in the nucleus after exposure to PI's resulting in excess fatty acid synthesis in the liver and hepatic steatosis [17, 18]**.** In the adipose tissue there is an enzyme called lipoprotein lipase which causes lipolysis of chylomicrons in the exogenous pathway of lipid metabolism which results in uptake of dietary TAG. PIs impair lipoprotein lipase (LPL)

activity with a concomitant rise in TAG's through inhibition of lipolysis and failure of lipid uptake by adipocytes [19]**.** PI's also reduce peroxisome proliferator-activated receptor gamma (PPARγ) expression which is a nuclear receptor crucial for differentiation of adipocytes and a prime transcription target of SREBP-1. Nuclear localization of SREBP-1 due to PI's activity may compromise further the PPARγ activity in the adipocytes of individuals on HAART. NRTIs have been shown to accumulate in adipocytes resulting in mitochondria dysfunction and depletion [20-22]due to their ability to inhibit DNA polymerase γ and induce dyslipidaemia over a longer period of time than PIs**[22].** Ultimately, circulating FFA increases [23], adiponectin secretion is reduced [24] and lipids accumulate in non-adipose tissues like the liver [25] due to abnormally functioning subcutaneous adipose tissue and reduced storage capacity. However, there is scarce data on these trends in dyslipidaemias in HIV naïve individuals of HAART within the sub-Saharan Africa which necessitates investigations into this particular sub-population with high prevalence of the HIV/AIDS (acquired immune deficiency syndrome) infections.

The scaling up of antiretroviral therapy (ART) in low and middle-income countries has transformed national AIDS responses and generated broad-based health gains. This has resulted in long term use of ART which has improved the health of HIV infected individuals. However, use of ART has also resulted in development of other conditions such as dyslipidaemia and lipodystrophy. Lipodystrophy is usually diagnosed clinically by accumulation of fat tissue in various parts of the body while dyslipidaemia is usually diagnosed using lipid profiles. Laboratory tests for lipid profiles are not done on routine monitoring of patients on ART treatment. There is a paucity of data on the lipid profiles of patients who visited Mpilo Central Hospital Opportunistic Infections Clinic except for those who had been suspected of dyslipidaemia by clinicians. This study determined the effect of gender, viral load, CD4 count, period of therapy and drug regimen on the lipid profiles of

patients on routine monitoring at Mpilo Central Hospital Opportunistic Infections Clinic. The lipid profiles, viral loads, CD4 counts were estimated using current methodologies available from manufacturers of equipment and materials. The convenience and accessibility of these methods persuaded the researchers to use these instead of other robust methods like polymerase chain reaction methods that will determine lipoprotein mRNA and other proteins which could show the effects of treatment at microstructure levels. These methods are not influenced by food intake greatly. However, we hypothesized that combined effects of HAART might also be associated with dyslipidaemia which necessitates routine monitoring of these profiles as the current practice and the prohibitive cost associated with lipid profiles negated such practice in life-long HIV/AIDS management.

MATERIALS AND METHODS

Ethical and legal considerations

Permission to carry out the study was sort from the research board at Mpilo Central Hospital. It was approved through the clinical director authorization. Approval was granted by the department of Opportunistic Infections Clinic (OIC). Access to study information was restricted to research team and research authorities. All data was kept under lock and key for the duration and after the study.

Participants informed consent:

Where necessary, all individuals were given a written informed consent to take part in the study. They were informed of their rights to withdraw from the study at any time. All participants' names and identification were removed from the data obtained in the study. De-identification of participants was done in the laboratory by assigning a unique number to each

client sample upon arrival for processing. No financial rewards were issued to the participants before or after the study. The researchers declared no conflict of interest in this study.

Study site

The study was conducted at Mpilo Central Hospital Opportunistic Infections Clinic in Bulawayo. It is a reference public health facility in the southern region of Zimbabwe with a large catchment area both from urban areas and rural areas. The clinic offers voluntary HIV counseling and testing (VCT), ART and limited community outreach services to patients on ART.

Study design and participants

A cross sectional study was done involving HIV infected patients of age between 17 years and 52 years receiving ART and returning for their six-monthly laboratory check-up between May 2018 and July 2018 using convenience sampling. Lipid profile was not included in the subsidized laboratory tests offered as part of a routine measurement in the clinic. Prior to sample collection, sociodemographic, clinical, laboratory and treatment related variables of interest were collected from medical records. Blood samples were collected in the mornings after an overnight fasting and centrifuged at 3000 g per minute for 30 minutes. The plasma obtained was stored at -20°C and later used for lipid assays.

Study participant's data

Patient's data was collected from the clinical records beginning with the inception of HAART (baseline). HAART treatment is defined as any combination of no less than three antiretroviral drugs including a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitors (NNRTIs). General demographic and epidemiological data (date of birth, gender, date of first positive HIV test) were obtained from the records.

Inclusion criteria

Patients aged between 17 years and 52 years with complete medical history. This age group was considered as able to give consent, where applicable, and permission to perform phlebotomy on participants in the study.

Exclusion criteria

Patients below the age of 16 and above 60 years were excluded from the study. These age groups, although the most affected by the disease, have confounding factors that are associated with both young age and elderly. The wider physiological variations are seen in the pediatrics and the geriatrics.

Laboratory analysis

Lipid profiles analysis

A blood specimen was drawn into a red top vacutainer blood collection tube. It was allowed to stand for 45 min at room temperature for complete clotting and clot retraction. A shorter period may result in incomplete clotting and secondary clots may form later. During the clotting period the collection tube was left sealed. The tube was then centrifuged at 1,500 x g for 30 min. Sample serum was extracted into serum cups and kept frozen at -20°C, in a freezer until shipped to the laboratory. Total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDLC) serum levels were measured by enzymatic methods using the Mindray BS 300 analyser (Mindray Medical, Warszawa, Poland) using the manufacturer's protocol. Dyslipidemia was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, 2004 as the occurrence of any one of the following conditions: TC >5.17 mmol/l (>200 mg/dl), LDL-C >3.16 mmol/l (>130 mg/dl), and HDL-C <1.03 mmol/l (<40 mg/dl) for males, <1.30 mmol/l (<50 mg/dl) for females.

CD4count

CD4 count was conducted on samples collected in EDTA coagulant containing tubes using BD FACSCount™ Flow Cytometer (BD Biosciences, California) by incubating anti-coagulated whole blood with monoclonal antibodies to the various cellular antigens that identify specific cell populations (phenotypes) and then lysing the blood to remove red blood cells. The antibodies were conjugated to fluorescent tags that emit light of a certain frequency when excited by a laser beam. The specimens were analyzed on a flow cytometer to determine the proportion of cells of a particular phenotype (that emit light at the right wavelength).

Viral load

Determination of patient viral load was done on blood specimens collected in sample tubes containing EDTA anticoagulant. The samples were centrifuged at 3000g for twenty minutes then plasma was separated from the cell components. The plasma was stored at -20^{o}C as the samples were being batched. Viral load test was perfomed using COBAS® AmpliPrep / COBAS® TaqMan® system (Roche Diagnostics, Indianapolis, IN USA).

Statistical Analysis

Statistical analysis was performed using GraphPad Prism version 5.02 and Microsoft Excel (2013). Data was tested for normality using the Shapiro-Wilk test and non-parametric data was analysed using Mann-Whitney U test. All data was expressed as mean ± standard deviation (SD). $P<0.05$ was considered as statistically significant.

RESULTS

Table 1 Baseline characteristics of study population

Variables	Number (%)
(n = 149)	
Gender:	
Male	65 (36.9)
Female	94 (63.1)
Age group (Years):	
17-25	29 (19.5)
26-35	30 (20.13)
35+	90 (60.40)
CD4 Count (cells/µL):	
<350	33 (22.15)
350-499	34 (22.89)
500+	82 (55.03)
Duration of ART (Weeks or months):	
<24	44(29.5)
25-52	43(28.9)

>52	62(41.6)
Viral load (copies/ml):	
<40	96(68.6)
>40	44(31.4)
Drug regimen:	
PI regimen	14(9.4)
NNRTI regimen	135(90.6)

Viral load was <40 in the majority (68.6%) of the participants. Most (55%) respondents had CD4 >500. More females (63.1%) were on HAART and were aged>35 (60.4%) years. NNRTI (90.6%) were the more commonly prescribed HAART; the majority (41.6%) had been on HAART for the duration of greater than 52 weeks.

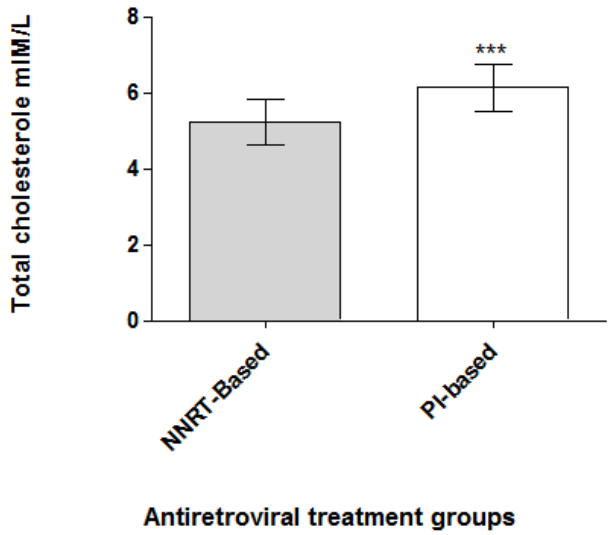

Figure 1: Total cholesterol in NNRTI based and PI based regimen. PI-based TC significantly higher than NNRT (***p = 0.001)

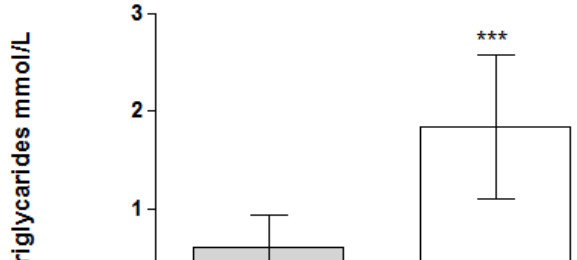

Figure 2: Triacylglycerols in NNRTI based and PI based regimen. PI-based TAG significantly higher than NNRT (***p = 0.001)

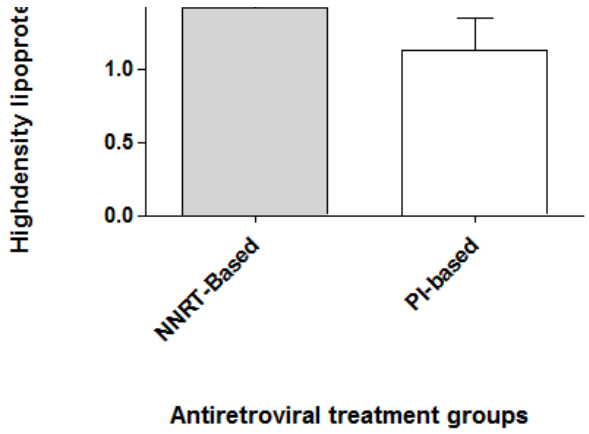

Figure 3: High Density Lipoproteins in NNRTI based regimen and PI based regimen.PI-based HDL significantly higher than NNRT (****p = 0.0001)

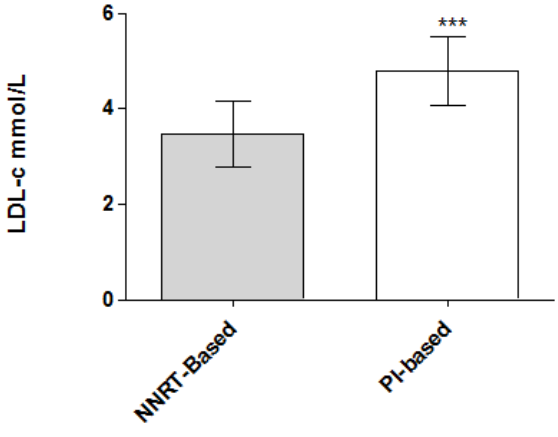

Figure 4: Low Density Lipoproteins on NNRTI based regimen and PI based regimen. PI-based LDL-c significantly higher than NNRT (***p = 0.001)

Table 2: Effects of treatment on study variables

Parameters	**Antiretroviral drug groups**		
	NNRT-Based	**PI-Based**	**P value**
VLDL-c	0.28±0.16	0.84±0.33[a]	0.0001
Non-HDL	3.81±0.61	5.00±0.68[a]	0.0001
Total cholesterol/ HDL ratio	3.84±0.85	5.61±1.16[a]	0.0001
Creatinine	66.46±19.58	80.87±22.41	0.0212
Hb	12.26±2.62	12.63±2.57	0.8461
CD4 count	547.2±268.6	425.8±328.3	0.0738
Viral load	11233±53065	6679±13595	0.5781

PI-based VLDLc vs NNRT-based VLDLc significantly higher (*p = 0.05); PI-based Non-HDL significantly higher compared to NNRT-based Non-HDL (*p = 0.05); Total

Cholesterol/ HDL ratio significantly higher for PI-based compared to NNRT-based (*p = 0.05); PI-based Creatinine significantly higher for PI-based compared NNRT-based (*p = 0.05).

Table 3 Factors associated with dyslipidemia

	TC> 5.2mmol/l (%)	TAG > 2.0mmol/l (%)	HDL < 1.0mmol/l (%)	VLDL > 0.6mmol/l (%)	LDL > 3.0mmol/l (%)	TC/HDL ratio > 4.1 (%)

Sex						
Male	**26 (36)**	**2 (25)**	**4 (36)**	**8 (47)**	**41 (36)**	**22 (35)**
Female	**46 (64)**	**6 (75)**	**7 (64)**	**9 (53)**	**74 (64)**	**41 (65)**
Age group						
17 – 25	**13 (18)**	**2 (25)**		**5 (29)**	**22 (19)**	**13 (20)**
25 – 34	**13 (18)**		**2 (18)**	**3 (18)**	**21 (18)**	**10 (15)**
>35	**46 (64)**	**6 (75)**	**9 (82)**	**9 (53)**	**72 (63)**	**42 (65)**
CD4 count						
< 350	**17 (25)**	**2 (33.3)**	**3 (27)**	**6 (38)**	**25 (23)**	**17 (27)**
350 – 499	**14 (21)**	**2 (33.3)**	**2 (18)**	**5 (31)**	**24 (22)**	**11 (18)**
>500	**36 (54)**	**2 (33.3)**	**6 (55)**	**5 (31)**	**59 (55)**	**34 (55)**
Viral load						
< 40	**46 (68)**	**1 (25)**	**5 (45)**	**5 (45)**	**43 (62)**	**23 (59)**
>40	**22 (32)**	**3 (75)**	**6 (55)**	**6 (55)**	**26 (38)**	**16 (41)**
Time on ART						
< 24 weeks	**19 (27)**	**1 (17)**	**2 (18)**	**1 (6)**	**32 (28)**	**18 (28)**
25 – 52	**17 (24)**	**2 (33)**		**3 (18)**	**30 (26)**	**15 (23)**
>52	**35 (49)**	**3 (50)**	**9 (82)**	**13 (76)**	**54 (47)**	**31 (48)**
ART regimen						
PI regimen	**59 (82)**	**6 (100)**	**4 (36)**	**11 (65)**	**13 (11)**	**12 (19)**
NNRTI regimen	**13 (18)**	**0**	**7 (64)**	**6 (35)**	**102 (89)**	**52 (81)**

DISCUSSION

The baseline characteristics of the patients shows that most patients were females compared to males. This shows that more women visited the clinic for routine laboratory checkup than

men. This was consistent with findings in a study done in Cameroon [26] where they reported 72.8% being female patients. The prevalence of HIV infection is reported to be higher in females as compared to males. Total cholesterol greater than 5.2 mmol/L was found more in males compared to women.

The study demonstrated a high prevalence of dyslipidaemia (77%) in HIV-patients receiving ART who visited the clinic for routine laboratory-based checkups. Raised levels of LDL-c and hypercholesterolaemia were the most common forms of dyslipidaemia. This was predominant in women than in men which may be due to the high number of females included in the study. Hypertriacyglycerolaemia, raised levels of VLDL-c as well as low levels of HDL-c was found in a few patients grouped according to gender. Women were associated with a greater risk of lipid disturbances than men though our study lacked the evidence to support this association. Increasing the power of our study and adjusting for body mass index could have improved our probability of detecting the sex difference. However, this finding is coherent with current knowledge that women experience more ART-induced (metabolic) adverse effects than men[27].

The patients in the study group were also grouped according to age group for analysis of results. The minimum age of participants was set at 17 years to limit other factor that may influence laboratory results due to patient physiological processes determined by age. Also the maximum age limit was set at 52 years for the study participants. The majority of the participants were between 17 years and 25 years but overall, those above 35 years contributed 60.4% of the study group. As age increases, proatherogenic lipid parameters also increase. In this study, it appeared that younger persons below the age of 25 years were at lower risk of dyslipidaemia. There was no pattern for the association between age and abnormal lipid profile hence need for a larger study population as the frequency is following the proportional

representation of participants. Low number of participants in our study might have been responsible for the inability to detect any significant relationship.

Participants were also grouped according to their CD4 count which is measured to determine the immune response of HIV infected patients. The majority of the participants had CD4 count greater than 500cells/μL showing relevant immune activation and possible viral suppression. In other studies, severe immune suppression (low CD4 count) has been associated with dyslipidaemia in ART-naive HIV infected persons [28]. However, in a cohort of persons doing well on highly active antiretroviral therapy (HAART) with a sufficiently improved mean CD4 count, there is little variability in CD4 count of the group and therefore a difference in dyslipidaemia cannot be attributed to differences in CD4 counts [29]. The latter is the case in our study and in other studies involving patients on HAART [26].

It was important to also characterize the study group according to the duration of treatment. This was reviewed in literature to have an effect on the lipid profiles on patients depending on the drugs being taken. In this study participants were grouped according to number of weeks on treatment. The majority of the study population had been on medication for more than 52 weeks. In other studies it was reviewed that HAART is associated with a cardio-protective lipid profile in the short term [26] because after initiation of ART, lipid levels return to baseline levels but soon they rise above pre-seroconversion levels in the long term [26]. In this study there was no significant difference in the lipid profiles. This may be due to the time limits applied as well the number of participants. Patients were also tested for levels of viral load. Most participants had a viral load of less than 40 copies/ml of blood. The recommended treatment regimen for HIV being used is the combination of three or more antiretroviral drugs to effectively reduce the viral load. In Zimbabwe, the ART regimens mostly used are nucleotide reverse transcriptase inhibitors (NRTIs) such as tenofovir in combination with non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as

nevirapine or in combination with protease inhibitors such as lopinavir and ritonavir, together known as Kaletra/Alluvia[30]. There is conflicting evidence from studies performed in both African and Western countries as to whether ART induces dyslipidemia[31]. According to the patient database at the clinic, NRTI drugs were common in all participants with either an NNRTI or PI being added. In this study most participants were on NNRTI treatment. Noteworthy is the finding of a significantly prominent serum creatinine amongst the PI-based as compared to the NNRT-based regimens regardless of the disparity in participant numbers in the former. This may mean the existence of an association between renal insufficiency and dyslipidaemias in HIV/AIDS HAART naïve participants. Higher accumulation of LDL cholesterol in PI-based participants may invariable indicate renal retention as macromolecules in participants with compromised renal function and or hepatic compensation. This may also indicate Apo E polymorphism and or genetic variation in handling of lipid metabolism in clients on HAART, an aspect that needs further elucidation. Indeed, Apo E has been known to influence lipid profiling and dyslipidaemias in other subpopulations which are not necessarily HAART naïve HIV/AIDS prone.

CONCLUSION

This is the first study to be done on patients visiting the clinic on a local population. Lipid profiles are also affected by environmental factors therefore it was crucial to obtain accurate information on effects of HAART on local population for decision making. Most patients who were on NNRTI regimen had higher TC and slightly elevated HDL-c while those on PI based regimen had elevated TC and TAG. There was no much difference in lipid profiles when compared to CD4 counts of the patients. The number of weeks on HAART also affected the lipid profiles as revealed in this study. The study mainly consisted of female participants hence there was a larger number of them with dyslipidaemia as compared to their

counterparts. Dyslipidemia was observed in the study. The viral load difference also did not affect the lipid profiles significantly as revealed by this study. Lipid profiles must be included in routine laboratory monitoring of patients on HAART as evidenced by the number of people affected. It is recommended that further investigations been done in various aspects to give more information on the combined effects of HAART on lipid profiles. Genetic factors also contribute to lipid metabolism with genes like the ApoE being associated with dyslipidaemia. It is important to determine the environmental factors that affect lipid profiles among the local population to understand the effects of HAART. Also, serum creatinine is a critical marker of renal insufficiency, a condition that may influence greatly lipid metabolism homeostasis in HIV/AIDS-HAART combination. There is need to monitor patients over a long period of time for consistent medication.

LIMITATIONS

The study was influenced by selection bias with more females than males due to differences in the health-seeking behaviors of men and women at the clinic. There was lack of HIV infected patients who are treatment naïve to compare with as all diagnosed patients are put on treatment as per government regulation as advised by the local clinicians. No study had been done to determine the reference ranges of lipid profiles on the local population as it is affected by environmental factors. There is need to determine levels of lipid profiles that defines dyslipidaemia as this study used literature determined on subjects in United States of America which are subjected to different environmental factors. Due to limited resources the sample size was small with most patients being on NNRTI regimen compared to PI regimen.

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